II. REMARKS/ARGUMENTS

A. Regarding the Amendments

Claim 2 has been cancelled. Claim 1 was amended to more specifically point out that the affinity matrix used in the method of the present invention comprises a fibroblast growth factor that preferentially binds to anticoagulant heparin or heparan sulfate compared to non-anticoagulant heparin or heparan sulfate. This amendment is supported by the application as a whole, and particularly by original claim 2. Claims 1 and 3-26 are pending in the application. During a telephone interview dated March 16, 2004, the Examiner indicated that claims 16-26 stand withdrawn.

B. Rejections under 35 U.S.C. § 102

1. The Habuchi reference.

The Examiner rejected claims 1, 2, 9, 10, 12 and 15 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,849,722, by Habuchi et al. Specifically, the Examiner alleges that Habuchi discloses instant claim 1 because Habuchi uses bFGF-Sepharose affinity matrix to separate the bound and unbound fractions of heparin/heparan sulfate. The Examiner contends that Habuchi anticipates claim 2 because the Examiner believes that Habuchi's method preferentially binds to anticoagulant heparan sulfate compared to non-anticoagulant heparan sulfate. The Examiner noted that he considers the heparan sulfate that binds to the bFGF-sepharose to be anticoagulant heparan sulfate because anticoagulant activity is an inherent property of heparan sulfate. Applicants respectfully traverse.

Habuchi is directed to a method for preparing oligosaccharides derived from heparan sulfate that have a high affinity for fibroblast growth factor but that do not react with antithrombin III, heparin cofactor II, platelet factor 4. *See*, col. 1, ll. 11-15. These oligosaccharides are desirable precisely because they lack anticoagulant activity. *See*, col. 2, ll.

3-6 and col. 7, ll. 55-64. Applicants acknowledge that Habuchi describes contacting heparan sulfate with a bFGF-Sepharose affinity matrix to produce bound and unbound fractions of heparan sulfate. See, e.g., cols. 4 - 6. However, there is nothing in the disclosure that suggests that the affinity matrix of Habuchi preferentially binds to anticoagulant heparan sulfate compared to non-anticoagulant heparan sulfate.

The Examiner is mistaken to assume that the heparan sulfate that binds to the bFGF-Sepharose is anticoagulant heparan sulfate. It is known in the art that only a portion of heparin and heparan sulfate possess anticoagulant activity. *See*, instant specification, p. 3, ll. 5-10; *see, also*, U.S. Patent 5,034,520 (cited by the Examiner) col. 1, ll. 34-36 (teaching that two-thirds of heparin chains lack anticoagulant activity). Habuchi clearly does not teach an affinity matrix that preferentially binds heparan sulfate that is anticoagulant, particularly in light of the fact that the whole point of Habuchi is to isolate oligosaccharides that are not anticoagulant. . In fact claim 5 is specifically directed to "an oligosaccharide with affinity for fibroblast growth factor (FGF) and no reactivity with antithrombin III and heparin cofactor II" i.e., to heparin that lacks anticoagulant. Habuchi does not teach an element of claim 1, as presently amended, and therefore does not anticipate claim 1, nor any of the claims dependant there from. Habuchi does not anticipate claim 15, for the same reasons as stated above.

2. The Lormeau reference.

The Examiner rejected claims 1, 6, 7, 8, 10, 11, 13, and 14 under 35 U.S.C. 102(b) as allegedly being anticipated by U.S. Patent No. 5,034,520, by Lormeau et al. Specifically, the Examiner stated that Lormeau discloses the method of claim 6 wherein the mixture of heparins comprises heparin that is not anticoagulant and heparin that is anticoagulant. The Examiner noted that Lormeau discusses a sub-fraction constituting fragments of heparin that possess the AT III binding site and exhibits a weak overall anticoagulant activity. Lormeau also discusses a

sub-fraction that completely lacks overall anticoagulant activity. The Examiner contends that Lormeau anticipates claims 7 and 8 because the mixture comprises crude heparin and low molecular weight heparin because the Examiner considers the mixtures of Lormeau to comprise a crude mixture of heparins that are low molecular weight. Applicants respectfully traverse.

Lormeau does not anticipate the present claims because Lormeau does not disclose an affinity matrix that preferentially binds the portion of heparin/heparan sulfate that is anticoagulant. In fact, Lormeau demonstrates why the present invention is novel and useful. Lormeau states that it is desireable to start with preparations of glycosaminoglycans that do not contain the binding site for AT III (i.e., which are not anticoagulant). *See*, col. 5, ll. 7-10. Lormeau has to separate the anticoagulant heparin from the non-anticoagulant portions and requires a two step process to do so. First, Lormeau uses a chromatography column equipped with a growth factor (i.e., FGF) supported on SEPHAROSE to separate glycosaminoglycans by their molecular weight. *See*, col. 5, *and see also* corresponding Example 8 at col. 16, ll. 30-42. Importantly, this affinity matrix does not preferentially bind heparin that is anticoagulant. Rather, it separates heparin as a function of molecular weight. *See*, col. 5, ll. 52-57. Lormeau specifically states that while the fraction recovered is homogeneous with regard to molecular weight, it is very heterogeneous with regard to ionic charge. *See*, col. 5, ll. 66-68. An additional step is required to separate the heparin that lacks the AT III binding site from the heparin that possesses the binding site. This is accomplished by depolymerization of heparin, followed by fractionation. *See*, col. 6, ll. 1-9. This required second step is described in Examples 9 - 11. *See*, cols. 16-18. The fractionation process involves chemical treatment and chromatography on Sepharose (not FGF-Sepahrose). *See*, id.

It is clear that the FGF affinity matrix of Lormeau does not preferentially bind heparin that is anticoagulant because Lormeau specifically states that the heparin separated using that matrix must be further fractionated to obtain the desired non-anticoagulant heparin. . In fact, claim 4 is specifically directed to "the mixture of glycosaminoglycans contains chains of saccharide residues which do not have a binding site for AT III", i.e., glycosaminoglycans that lack anticoagulant activity. In contrast, the present invention utilizes specific FGF that preferentially binds anticoagulant heparin, so that further fractionation is not required to isolate the anticoagulant heparin. *See*, Example 2 of the instant application. Applicants respectfully request that the rejection under U.S.C. §102(b) over Lormeau be withdrawn because Lormeau does not teach an FGF affinity matrix that preferentially binds the fraction of heparin/heparan sulfate that possesses anticoagulant activity.

C. Rejections under 35 U.S.C. § 103

1. The Habuchi reference.

The Examiner rejected claims 1 and 3 under 35 U.S.C. 103(a) as being obvious in view of Habuchi. Specifically, the Examiner stated that because Habuchi teaches a bFGF-Sepharose affinity matrix, it would be obvious you use FGF7. Applicants respectfully traverse.

As stated above, there is no evidence that the Habuchi affinity matrix preferentially binds anticoagulant heparan sulfate, and in fact the point of Habuchi is to isolate oligosaccharides that lack anticoagulant activity. In contrast, the present claims are directed to an FGF affinity matrix that preferentially binds anticoagulant heparin.

The Examiner should not assume that the affinity column of Habuchi preferentially binds anticoagulant heparan sulfate. Not all heparin/heparan sulfate is anticoagulant; in fact, two-thirds of it is not. *See*, Lormeau, col. 34-36. Likewise, even though it is known in the art that heparin/heparan sulfate has an affinity for FGF generally, the art does not teach affinity matrices

of particular FGFs, such as FGF7, that preferentially bind the anticoagulant portion of heparin/heparan sulfate. At the time of the present invention, it was not obvious in the art that certain members of the FGF family, of which now 22 are known, would have specific affinity for anticoagulant heparin, a property for which FGF7 is a prototype. Not all of the FGF family possesses this specificity for the anticoagulant portion of heparin/heparan sulfate. Example 2 of the instant specification demonstrates that an affinity matrix of FGF1 fails to enrich the anticoagulant activity of crude heparin, whereas FGF7 does enrich the anticoagulant activity. Likewise, the affinity matrix of bFGF-Sepharose used by Lormeau yields fractions that lack anticoagulant activity. *See* discussion above. It would not be obvious to use FGF7 specifically to obtain anticoagulant activity, because the art does not teach the beneficial result that FGF7 preferentially binds the anticoagulant portion of heparin/heparan sulfate. Applicants therefore request that the rejection under 35 U.S.C. §103(a) over Habuchi be withdrawn because Habuchi fails to teach or suggest an element of the present claims, namely, that the affinity matrix preferentially binds to anticoagulant heparin or heparan sulfate compared to non-anticoagulant heparin or heparan sulfate.

2. The Lormeau reference.

The Examiner rejected claims 1, 13, and 14 under 35 U.S.C. 103(a) as being obvious in view of Lormeau. Specifically, the Examiner alleges that it would be obvious to recover the anticoagulant heparin and to elute the anticoagulant heparin. Applicants traverse.

As described above, it was not obvious in the art that certain members of the FGF family, of which now 22 are known, would have specific affinity for anticoagulant heparin, a property for which FGF7 is a prototype. Lormeau fails to teach or suggest an affinity matrix that specifically binds to anticoagulant heparin or heparan sulfate compared to non-anticoagulant heparin or heparan sulfate. Lormeau makes it clear that the bFGF-Sepharose column separates

heparin on the basis of molecular weight, not anticoagulant activity. Further, the goal of Lormeau is to obtain glycosaminoglycans that lack anticoagulant activity. There is no suggestion to recover or elute the anticoagulant heparin; and even if there were, there is no teaching of how to obtain an affinity column that specifically binds to anticoagulant heparin or heparan sulfate compared to non-anticoagulant heparin or heparan sulfate. Applicants request that the rejection under 35 U.S.C. §103(a) over Lormeau be withdrawn.

D. Allowable subject matter

The Examiner indicated that claims 3 and 4 are allowable if they do not depend on a rejected claim and are rewritten in an acceptable form. The Examiner stated that the relevant art does not teach a fusion protein, and specifically a glutathione-S-transferase-FGF7 protein, as described in claims 3 and 4. Applicants assume that the Examiner is actually referring to claims 4 and 5, as these are the claims that deal with the discussed subject matter. In either case, Applicants respectfully thank the Examiner for acknowledging allowable subject matter, and urge that the rest of the claims now be allowed, in light of the present amendments and clarification.

No fees are believed to be due in connection with the filing of this Amendment and Response, however should be required for any reason relating to the enclosed materials, the Commissioner is authorized to deduct said fees from Deposit Account No. 01-2508/12740.0232.NPUS01.

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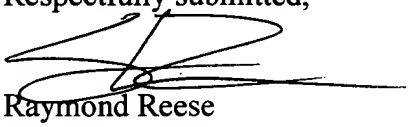
The Examiner is invited to contact the undersigned patent agent with any questions or comments related to the enclosed materials.

Respectfully submitted,



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Date: March 18, 2004